QA0237 DIV 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF **KATERINA LEFTHERIS, ET AL**
FOR: **NP TITLE - METHODS OF TREATING P38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS**
DIV TITLE - METHODS OF TREATING P38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS
APPLICATION NO: **10/696,178**
APPLICATION DATE: **10/29/2003**
ART UNIT: **1616**
EXAMINER: **PRYOR, ALTON NATHANIEL**
CONFIRMATION NO: **6531**
USPTO CUSTOMER NO: **23914**

TRANSMITTED VIA EFS-WEB

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. §1.56, applicant wishes to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

Each reference was cited in a foreign office action; copies of these references and the search reports are enclosed within.

Pursuant to the OG Notice of August 5, 2003 for U.S. national applications filed after June 30, 2003, the requirement for submitting a copy of each cited U.S. patent and each cited U.S. patent application publication is waived, copies of the U.S. patent and U.S. patent publications are not submitted. Copies of foreign patent documents and non-patent literature, if cited, are enclosed"

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form.

Applicant believes that there is no fee required with this filing of this paper. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Statement under 37 C.F.R. §1.97(e)(1)

I, the undersigned attorney, hereby state that each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

Respectfully submitted,

Bristol-Myers Squibb Company
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Date: Feb. 8, 2008

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January 3, 2008

By E-mail: patents@bms.com
DEADLINE: FEBRUARY 29, 2008

BRISTOL- MYERS SQUIBB COMPANY
Attn: Mr. Stephen B. Davis
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Princeton, NJ 08543-4000
UNITED STATES

REF: **BRISTOL- MYERS SQUIBB COMPANY**
Colombian Patent Application No. 03 039.926
International Patent Application No. PCT/US01/49982
Your Ref: 60/249,877 – QA0237
Our Ref: 90.907

Dear Mr. Davis,

We wish to inform you that the Patent Office's Examiner made a thorough examination on the above referenced patent application and stated the following observations:

1. CLARITY OF THE APPLICATION

The title must be amended such that it doesn't refer to treatment methods but to pyrrolotriazine compounds and their derivates, since according to Article 20 of Decision 486 treatment methods are not patentable.

Claim 7 is not concise when using terms such as "alkyl, substituted aryl and heteroaryl". Similarly, the substituents of formula (II) each have several different meanings, and correspond to a wide range of compounds, thus it is possible to patent a very large number of compounds different to formula (II); therefore, this would not be limiting the subject matter seeking protection with the patent application.

The compounds of claim 20 are within the scope of the compounds of claim 7, the applicant is advised to amend the set of claims such that claim 20 and its dependent ones are all dependent of claim 7.

2. EXCEPTIONS TO PATENTABILITY

Claims 1 to 6, 30 and 31 relate to methods for treating conditions associated with the activity of kinase p38, comprising administering an effective amount of compounds of formula (I) and (II), which is not patentable according to Article 20d) of Decision 486.

3. DETERMINATION OF THE STATE OF THE ART

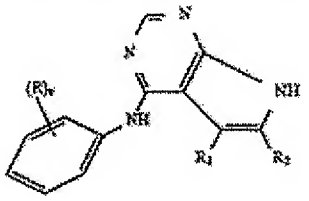
Once the available data sources were consulted, the following documents were found, dated before the claimed priority date and related to the application's subject matter.

N°	Document	Publication Date	Affected Claims	Affected Requisite
D1	US 5686457	1997.11.11	7 to 29	Inventive Step
D2	EP 0713876	1996.05.29	7 to 29	Inventive Step

NOT CITED
✓ cited in US Div

4. ASSESSMENT OF INVENTIVE STEP

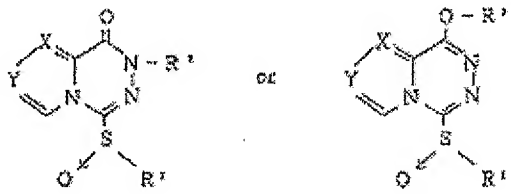
D1 is the closes anteriority, it describes compounds of formula:



These compounds have a structural formula similar to that of compounds of formula (II) of current claim 7 of the instant application and are also inhibitors of kinase proteins, so they are useful for treating different diseases involving these enzymes, such as inflammatory diseases, autoimmune disease and proliferative disorders.

The compounds described in D1 are only differentiated from the ones in the instant application by substituent Y of the amine in position 5 and the pyrrolopyrimidine ring at the nitrogen's position on the pyrrol ring fused to the pyrimidine ring which, in the application, forms a pyrrolotriazine whereas in the anteriority forms a pyrrolopyrimidine.

Document D2 describes compounds of general formula:



(Ia) (Ib)

By making the appropriate replacements on formula (1b), you can form compounds with a pyrrotriazoline nucleus that only differ from the ones in the present application in the position of the Nitrogen atoms of the six-member ring fused to the pyrrol ring and the substituents thereof. The compounds described in D2 also inhibit enzymes such as kinases which inhibition is associated with treatment of multiple disorders, such as inflammatory and allergic disorders, autoimmune diseases and cancer.

These structural differences do not seem to provide the claimed compounds with am unexpected effect, improvement or advantage with respect to the ones in the state of the art, since they are still useful for treating disorders associated with the activity of kinases and not tests or assays are provided showing a greater efficacy of the compounds of the application, therefore they can be regarded as alternative compounds to those already known.

Taking into consideration the technical problem of the present application, which is the need to provide methods for treating conditions associated with the activity of kinase 38p and compounds that act like inhibitors of these enzymes, that can be used for treating inflammatory, autoimmune and allergic diseases, we can see that the information in any of the anteriorities would suggest the skilled technician, using his general knowledge, to synthesize compounds derived from pyrrolotriazine similar to the those disclosed therein to solve the problem in an obvious manner, therefore the subject matter lacks inventive step.

If the applicant believes the compounds in the present application are superior to those in the state of the art, he must provide data proving such claim.

The Patent Office has granted a term to present a reply, which expires on **FEBRUARY 29, 2008**, to present the corresponding clarifications, amendments and arguments to defend the present application. If no response is

filed within the mentioned term, the above referenced patent application will be denied by the Colombian Patent Office.

Therefore, we would appreciate receiving your comments and/or technical arguments which should be solid enough in order to help us overcome the objections of the Patent Office, with respect to the inventive step of the application, bearing in mind the prior art cited by the Examiner.

Very truly yours,

Carlos Hoyos R.
Maria Eugenia Vasquez
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Application No.	Rel.	Date
03 781 756.6 - 1216	L1678 EP	17.12.2007
Applicant: Bristol-Myers Squibb Company		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Europäisches Patentamt · European Patent Office · Office européen des brevets

James, Sonya
Primary Examiner
for the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)
D2

The examination is being carried out on the **following application documents:**

Description, Pages

1-62 as published

Claims, Numbers

1-11 filed with entry into the regional phase before the EPO

1. Cited documents

1.1. Reference is made to the following document; the numbering will be adhered to in the rest of the procedure:

D1: PATIL S.A. ET AL.: 'Synthesis of pyrrolo[2,1-f][1,2,4]triazine congeners of nucleic acid purines via the N-amination of 2-substituted pyrroles [1]' JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 31, July 1994 - August 1994, pages 781 - 786, XP001079097

1.2. The following document is cited by the examiner (see the Guidelines, C-VI, 8.3). A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D2: L. F. Audrieth and L. H. Diamond: "Preparation of N-Substituted Hydrazines by Modification of the Raschig Synthesis" Journal of the American Chemical Society vol. 76, October 5, 1954, pages 4869 - 4871.

2. Clarity and Conciseness (Art. 84 EPC)

2.1. Claim 3 of the present application is unclear because it appears to have the same scope as claim 2. It is noted that the term "kinase-inhibiting pharmaceutical compounds" is not considered to limit the scope of the claim in any way, so that claim 3 is considered to relate to a method of preparing any compounds of the formula I, and not only those compounds of formula I which have kinase-inhibiting activity.

That is, claim 3 is considered to be superfluous.

2.2. Should the applicant consider that there is indeed a difference in scope between claims 2 and 3, it appears that the conciseness of the claims could be improved by not repeating in claim 3 the definitions of groups which have the same definitions as in claim 2.

2.3. Claims 8 and 10 of the present application are currently formulated as being dependent on either claim 2 or claim 3. Since claims 2 and 3 are currently formulated as separate, independent claims, this formulation appears unclear. Dependent claims should be formulated as depending on only one independent claim.

3. Novelty (Art. 54 EPC)

3.1. The present application relates to a method for preparing N-aminated pyrrole compounds which are useful in the synthesis of pyrrolotriazine compounds.

3.2. The document D1 relates to the synthesis of pyrrolotriazine compounds, using N-aminated pyrrole compounds as intermediates, and is considered to be the closest prior art to the present application.

3.3. D1 discloses the reaction of pyrrole-2-carboxaldehyde with hydroxylamine-O-sulfonic acid (HOSA) in the presence of KOH as base, to form N-aminopyrrolonitrile (Scheme 1).

3.4. The difference between the subject-matter of claim 1 of the present application, and the known method of D1, is that in claim 1, chloramine is used for the amination instead of

HOSA.

3.5. Therefore, the subject-matter of claim 1 is considered to meet the requirement of novelty (Art. 54 EPC).

3.6. Claims 2-11 are dependent on claim 1 or relate to the same method of amination as claim 1. **Therefore, the subject-matter of claims 2-11 is also considered to meet the requirement of novelty (Art. 54 EPC).**

4. Inventive Step (Art. 56 EPC)

4.1. The difference between the subject-matter of claim 1 and the known method of D1 is discussed above.

4.2. The technical effect of this difference appears to be improved yield of the aminated pyrrole product.

4.3. That is, the problem to be solved by the present application can be considered to be to adapt the method of D1 so as to improve the yield of the aminated pyrrole compound.

4.4. Although chloramine is known in the art for the formation of hydrazines from primary amines (see, for example, document D2), there is no indication in the prior art to suggest that chloramine could be used to increase the yield of a reaction involving the N-amination of an aromatic nitrogen-containing compound such as a pyrrole.

4.5. That is, the solution provided by the applicant in claim 1 does not appear to be obvious to the person skilled in the art.

4.6. Therefore, the subject-matter of claim 1 of the present application is considered to meet the requirement of inventive step (Art. 56 EPC).

4.7. Claims 2-11 are dependent on claim 1 or relate to the same method of amination as claim 1. **Therefore, the subject-matter of claims 2-11 is also considered to meet the**

requirement of inventive step (Art. 56 EPC).

5. Further comments

5.1. The applicant is invited to file new claims which take account of the above comments.

5.2. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims In particular, attention should be paid to terms such as "prodrugs" (for example on page 21, line 3), which do not form part of the invention as claimed. Statements in the description which imply that the invention relates to compounds per se (for example on pages 10-11) should also be amended appropriately. Furthermore, terms such as "herein incorporated by reference in its entirety" and "incorporated herein by reference" should be removed from the description. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

5.3. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see Guidelines E-II, 1).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.